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Search Results - Record(s) 1 through 3 of 3 returned.

☐ 1. Document ID: US 5958409 A

L3: Entry 1 of 3 File: USPT Sep 28, 1999

US-PAT-NO: 5958409
DOCUMENT-IDENTIFIER: US 5958409 A

TITLE: Method for treating multiple sclerosis

DATE-ISSUED: September 28, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Turk; John Leslie	London	N/A	N/A	GBX
Baker; David	London	N/A	N/A	GBX
Feldmann; Marc	London	N/A	N/A	GBX

US-CL-CURRENT: 424/141.1; 424/145.1, 424/156.1, 514/2, 530/350

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 2. Document ID: US 5863786 A

L3: Entry 2 of 3 File: USPT Jan 26, 1999

US-PAT-NO: 5863786
DOCUMENT-IDENTIFIER: US 5863786 A

TITLE: Nucleic acid encoding modified human tnf.alpha. (tumor necrosis factor alpha) receptor

DATE-ISSUED: January 26, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Feldmann; Marc	Hammersmith	N/A	N/A	GBX
Gray; Patrick William	Bothell	WA	N/A	N/A
Turner; Martin John Charles	Ann Arbor	MI	N/A	N/A
Brennan; Fionula Mary	Hammersmith	N/A	N/A	GBX

US-CL-CURRENT: 435/252.3; 435/320.1, 435/69.1, 435/69.7, 536/23.4, 536/23.5

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 3. Document ID: US 5633145 A

L3: Entry 3 of 3 File: USPT May 27, 1997

US-PAT-NO: 5633145
DOCUMENT-IDENTIFIER: US 5633145 A

TITLE: TNF.alpha. receptor-derived binding protein

DATE-ISSUED: May 27, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Feldmann; Marc	Hammersmith	N/A	N/A	GBX
Gray; Patrick W.	Bothell	WA	N/A	N/A
Turner; Martin J. C.	Ann Arbor	MI	N/A	N/A
Brennan; Fionula M.	Hammersmith	N/A	N/A	GBX

US-CL-CURRENT: 435/69.1; 435/252.3, 435/320.1, 435/69.7, 536/23.4, 536/23.5

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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Term	Documents
FELDMANN-MARC$	0
FELDMANN-MARC.USPT.	3
FELDMANN-MARC$.USPT.	3

Display 10 Documents, starting with Document: 3

Display Format: CIT Change Format

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Search Results - Record(s) 1 through 1 of 1 returned.

☐ 1. Document ID: US 5741488 A

L2: Entry 1 of 1 File: USPT Apr 21, 1998

US-PAT-NO: 5741488
DOCUMENT-IDENTIFIER: US 5741488 A

TITLE: Treatment of rheumatoid arthritis with anti-CD4 antibodies in conjunction with anti-TNF antibodies

DATE-ISSUED: April 21, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Feldman; Marc	London	N/A	N/A	GB2
Maini; Ravinder N.	London	N/A	N/A	GB2
Williams; Richard O.	London	N/A	N/A	GB2

US-CL-CURRENT: 424/154.1; 424/130.1, 424/141.1, 424/143.1, 424/144.1, 424/145.1, 424/153.1, 424/158.1, 424/173.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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Term	Documents
MAINI-RAVINDER$	0
MAINI-RAVINDER-N.USPT.	1
MAINI-RAVINDER$.USPT.	1

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Search Results -

Term	Documents
TNF.USPT.	4620
TNFS.USPT.	94
TNFALPHA.USPT.	13
TNFALPHAS	0
METHOTREXATE.USPT.	6096
METHOTREXATES.USPT.	16
(METHOTREXATE SAME (TNFALPHA OR TNF)).USPT.	108

Database: US Patents Full-Text Database; JPO Abstracts Database; EPO Abstracts Database; Derwent World Patents Index; IBM Technical Disclosure Bulletins

Refine Search: `('tnf' or 'tnfalpha' ) same (methotrexate) and (arthritis or crohns)` Clear

Search History

Today's Date: 10/15/2000

DB Name	Query	Hit Count	Set Name
USPT	('tnf' or 'tnfalpha') same (methotrexate)	108	L4
USPT	feldmann-marc$	3	L3
USPT	maini-ravinder$	1	L2
USPT	feldmann-marc?	0	L1

WEST

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Main Menu | Search Form | Posting Counts | Show S Numbers | Edit S Numbers | Preferences

Search Results -

TNF.USPT.
TNFS.USPT.
TNFALPHA.USPT.
TNFALPHAS
METHOTREXATE.USPT.
METHOTREXATES.USPT.
ARTHRITIS.UG71;UG72,UG73,UG74,UG75,UG76,UG77,UG78,UG79,UG80,UG81,UG82,UG83,UG
ARTHRITI.UG71,UG72,UG73,UG74,UG75,UG76,UG77,UG78,UG79,UG80,UG81,UG82,UG83,UG8
CROHNS.UG71,UG72,UG73,UG74,UG75,UG76,UG77,UG78,UG79,UG80,UG81,UG82,UG83,UG84
CROHN.UG71,UG72,UG73,UG74,UG75,UG76,UG77,UG78,UG79,UG80,UG81,UG82,UG83,UG84,U
((METHOTREXATE SAME (TNFALPHA OR TNF)) AND ((CROHNS OR ARTHRITIS).CLMS.)).U:

Database: US Patents Full-Text Database; JPO Abstracts Database; EPO Abstracts Database; Derwent World Patents Index; IBM Technical Disclosure Bulletins

Refine Search: `('tnf' or 'tnfalpha' ) same (methotrexate) and (arthritis or crohns).clms.` Clear

Search History

Today's Date: 10/15/2000

DB Name	Query	Hit Count	Set Name
USPT	('tnf' or 'tnfalpha') same (methotrexate) and (arthritis or crohns).clms.	0	L6
USPT	('tnf' or 'tnfalpha') same (methotrexate) and (arthritis or crohns)	35	L5
USPT	('tnf' or 'tnfalpha') same (methotrexate)	108	L4
USPT	feldmann-marc$	3	L3
USPT	maini-ravinder$	1	L2
USPT	feldmann-marc?	0	L1

5/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

07923370 BIOSIS NO.: 000042010193
EFFECTS OF A WEEKLY DOSES OF **METHOTREXATE** ON IL-1 **TNF** AND IL-6 IN PATIENTS WITH RHEUMATOID **ARTHRITIS**
AUTHOR: BARRERA P; JANSSEN E M; BOERBOOMS A M T; VAN DE PUTTE L B A; SAUERWEIN R W; VAN DER MEER J W M
AUTHOR ADDRESS: UNIV. HOSPITAL NIJMEGEN, POSTBOX 9101, NETHERLANDS.
JOURNAL: THIRD INTERNATIONAL WORKSHOP ON CYTOKINES, STRESA, ITALY, NOVEMBER 10-14, 1991. CYTOKINE 3 (5). 1991. 504.
CODEN: CYTIE
DOCUMENT TYPE: Meeting
RECORD TYPE: Citation
LANGUAGE: ENGLISH

7/7/6 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07524313 93219728

[If I had chronic polyarthritis--current ideas on basic therapy]

Wenn ich eine chronische Polyarthritis hatte--Neue Ideen zur Basistherapie.

Hasler F

FMH Innere Medizin, speziell Rheumaerkrankungen, Chur.

Schweizerische Rundschau fur Medizin Praxis (SWITZERLAND) Mar 23 **1993**, 82 (12) p349-52, ISSN 0369-8394 Journal Code: SRM

Languages: GERMAN Summary Languages: ENGLISH

Document type: JOURNAL ARTICLE ; English Abstract

Rheumatoid **arthritis** (RA) is a chronic inflammatory disorder of largely unknown etiology and complex multifactorial pathogenesis. To date, the medical management has been less than optimal and has consisted primarily of drugs that modulate the acute inflammatory process. Over the years a treatment program referred to as the classical therapeutic pyramid has evolved. A new concept and a controversial one in therapy of RA is that already at the time of definitive diagnosis, a more concerted effort towards vigorous treatment using second-line drugs such as **methotrexate** , should be made. It is very likely that over the next 5 years interventions such as monoclonal antibodies directed against predetermined T-cell subpopulations and anti-cytokines such as **TNF-**

7/7/4 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

05619503 EMBASE No: 1994014905
The current and future therapy strategies of rheumatoid **arthritis** (RA)
GEGENWARTIGE UND ZUKUNFTIGE THERAPIESTRATEGIEN DER RHEUMATOIDEN **ARTHRITIS** (RA)
Schacht E.
Hauptabteilung Med. Wissenschaften, E. Tosse und Co. GmbH, Friedrich-Ebert-Damm 101,22047 Hamburg Germany
Zeitschrift fur Rheumatologie (Z. RHEUMATOL.) (Germany) 1993, 52/6 (365-382)
CODEN: ZRHMB ISSN: 0340-1855
DOCUMENT TYPE: Journal; Review
LANGUAGE: GERMAN SUMMARY LANGUAGE: GERMAN; ENGLISH

The triad of inflammation, immunoproliferation and synovial hyperplasiais recognized in the pathogenesis of rheumatoid **arthritis**, however, the sequence of events remains as highly controversial as ever. The 'RA pyramid' was established on the assumption that inflammation is at the top with the destructive processes as sequelae. The moderate successes achieved by conservative therapy with regard to long-term outcome cast doubt on this hypothesis. Inhibitors of prostaglandin synthesis have not been and are not disease modifying. Do substances which influence the endothelial adhesion molecules or leucocyte adhesion receptors (leumedines) promise to be more successful? Do the empirically developed disease modifying antirheumatic drugs (Gold parenteral, MTX) have to be administered earlier? Unfortunately, there is a need for a differential diagnosis which is prognostically valid with regard to the dynamics and aggressiveness of rheumatoid **arthritis**. Moreover, a pharmacological basis for optimally founded combination strategies is also lacking. Presently, the emphasis of research is directed at the regulation of dysfunctional immune systems. Immunosuppressives (cyclosporin A), cytokine antagonists, receptor antagonists and soluble cytokine receptors (IL-1, IL-6, **TNF-alpha**), antibodies against lymphocyte subgroups (CDinf 4, CDinf 7) or against cytokines and their receptors are part of the arsenal for the medium term. Too little is still known about the role of protective cytokines (TGF-beta, IL-4, gamma-INF). Currently, however, it is prognosticated that these targeted therapies will only succeed in RA subgroups or only in intelligent combinations. More attractive alternatives are strategic therapy modalities which intervene very early in the pathological process, such as the modulation of antigen presentation (MHC blocking peptides, T-cell receptor antagonists, T-cell vaccination) or the induction of tolerance against autoantigens through the oral administration of antigens (collagen II, HSP's, OM-8980). If the center of the pathological process, however, is found in the synovial proliferation of tumor-like cell clusters, then there are only a few years at the beginning of the disease when there is a real chance to impede destruction. In this case, aggressive induction therapy can be the only key to success. In the future, specifically active cytostatics (inhibitors of angiogenesis) will have to be developed and clinical trials conducted on adjuvant therapies with substances which strengthen bone and cartilage, making them more resistant to aggressive cell clusters (bisphosphonates, calcitonins, metalloproteinase- or collagenase-inhibitors).

09033807 BIOSIS NO.: 199497042177
Elevated levels of **TNF** in the joints of adjuvant arthritic rats.
AUTHOR: Smith-Oliver Tracey; Noel L Staton; Stimpson Steven S; Yarnall David P; Connolly Kevin M(a)
AUTHOR ADDRESS: (a)Dep. Immunology, Glaxo Res. Inst., Five Moore Drive, Research Triangle Park, NC 27709**USA
1993
JOURNAL: Cytokine 5 (4):p298-304 1993
ISSN: 1043-4666
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The primary purpose of this study was to determine whether local levels of tumor necrosis factor (**TNF**) were elevated in chronically inflamed joints in rats with adjuvant-induced **arthritis** (AA). We also wished to develop methodology for the quantitative measurement of joint **TNF**, and to examine the effects of known anti-inflammatory agents on joint **TNF** levels. **TNF** levels were measured in joints from AA rats taken during the systemic phase (day 20) of arthritic disease. Using the L929 bioassay, joint extracts from AA rats had significantly greater **TNF** levels (1054 +- 147 pg/g tissue) than joint extracts from normal rats (110 +- 42 pg/g tissue). Administration of ibuprofen failed to significantly inhibit **TNF** levels in the joint at a time point when paw swelling was significantly reduced. The immunomodulating agents, **methotrexate**, cyclosporin A (CSA) and HWA486 profoundly inhibited both joint **TNF** levels and paw swelling. The specificity of this assay for **TNF** was supported by studies with a polyclonal rabbit anti-mouse **TNF** antibody which neutralized 78-87% of the **TNF** activity in the joint extracts. Our studies demonstrate a quantitative increase in local **TNF** expression in adjuvant **arthritis** and support a role for **TNF** in chronic inflammation.

8/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09137190 BIOSIS NO.: 199497145560
Serum levels of interleukin-6 and tumour-necrosis-factor-alpha are not correlated to disease activity in patients with rheumatoid **arthritis** after treatment with low-dose **methotrexate**.
AUTHOR: Wascher Thomas C(a); Hermann J; Brezinschek R; Brezinschek H P; Wilders-Trusching M; Rainer F; Krejs G J
AUTHOR ADDRESS: (a)Dep. Med., Auenbruggerpl. 15, A-8036 Graz**Austria
1994
JOURNAL: European Journal of Clinical Investigation 24 (1):p73-75 1994
ISSN: 0014-2972
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Cytokines are major mediators of inflammatory responses in rheumatoid **arthritis**. Some of them have been shown to correlate with the disease activity and thus are proposed to be used for monitoring patients. Therefore the effects of a low-dose therapy with **methotrexate** on serum concentrations of interleukin-6 (IL-6) and tumour-necrosis-factor-alpha (**TNF-alpha**) were examined in eight patients with seropositive rheumatoid **arthritis**. Serum levels of IL-6 and **TNF-alpha** were significantly elevated in patients compared to healthy controls. Before the onset of MTX treatment IL-6 concentrations were correlated to the c-reactive protein (P lt 0.05) but the correlation was abolished after treatment. For **TNF-alpha** no correlations neither before nor after treatment were observed. Both cytokines remained substantially elevated after MTX treatment despite a clear reduction in disease activity. Thus we suggest that one of the effects of MTX might be the inhibition of some of the actions of IL-6 and **TNF-alpha**.

9/7/14 (Item 7 from file: 73)
DIALOG(R)File 73:EMBASE

06085795 EMBASE No: 1995116283

The pathogenesis of rheumatoid **arthritis** and the development of therapeutic strategies for the clinical investigation of biologics

Panayi G.S.
Arthritis and Rheumatism Council, Guy's Hospital,London United Kingdom

Agents and Actions Supplements (AGENTS ACTIONS SUPPL.) (Switzerland) 1995, 47/- (1-21)
CODEN: AASUD
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

This review discusses current concepts of the pathogenesis of rheumatoid **arthritis**. It is proposed that RA is a T cell mediated disease following which a large number of subsequent inflammatory events are unleashed. Many of the pathogenetic steps are targets for new therapies including biologics. Laboratory, clinical and radiological methods of assessing disease activity are sufficiently sensitive and reproducible to permit their use in multicentre studies capable of detecting a biologic with disease modifying activity. The clinical assessment of the efficacy and toxicity of biologics poses unique problems. These have been illustrated by the example of 3 monoclonal antibodies directed against ICAM-1, CD4 and **TNFalpha**. The main role of most biologics may be to pinpoint important therapeutic targets which can be attacked by more easily administered and less costly xenobiotic drugs.

/13 (Item 6 from file: 73)
DIALOG(R)File 73:EMBASE

06107129 EMBASE No: 1995137770

Long term treatment of rheumatoid **arthritis** with high doses of intravenous immunoglobulins: Effects on disease activity and serum cytokines

Muscat C.; Bertotto A.; Ercolani R.; Bistoni O.; Agea E.; Cesarotti M.; Fiorucci G.; Spinozzi F.; Gerli R.

Institute of Internal Medicine, University of Perugia, Policlinico di Monteluce,I-06100 Perugia Italy

Annals of the Rheumatic Diseases (ANN. RHEUM. DIS.) (United Kingdom) 1995, 54/5 (382-385)
CODEN: ARDIA ISSN: 0003-4967
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Objective - To evaluate the effects of long term treatment of rheumatoid **arthritis** (RA) with high doses of intravenous immunoglobulins (IVIg). Methods - Ten patients with active RA and prior unsuccessful treatment with at least one slow acting antirheumatic drug were treated with 400 mg/kg of IVIg for the first three days and then once a month for 12 months. Clinical evaluation and laboratory analysis were performed every month. Serum levels of tumour necrosis factor alpha (**TNFalpha**), soluble interleukin-2 receptor (sIL-2R), IL-1alpha, IL-1beta, IL-6 and interferon gamma (IFNgamma) were measured at baseline and at three monthly intervals for 15 months. Results - Although laboratory parameters were not influenced by the treatment, a late but significant clinical improvement was observed after six months. Serial measurement of cytokines revealed a rapid and persistent decrease in serum **TNFalpha** and a late and significant reduction in sIL-2R concentrations. Conclusion - This study suggests that IVIg can ameliorate the symptoms and improve the functional capability of RA patients. This effect is associated with a partial modulation of serum concentrations of inflammatory cytokines and, more interestingly, with a late decrease in sIL-2R which correlated with the late reduction in disease

9/7/9 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

06177679 EMBASE No: 1995213487
Biological therapies: A novel approach to the treatment of autoimmune disease
Fox D.A.
Division of Rheumatology, Department of Internal Medicine, Univ. of Michigan Medical Center,Ann Arbor, MI 48109-0358 United States
American Journal of Medicine (AM. J. MED.) (United States) 1995, 99/1 (82-88)
CODEN: AJMEA ISSN: 0002-9343
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Biological therapies for rheumatoid **arthritis** (RA) make use of molecules (including derivative and recombinant forms) produced by cells of the immune system or by cells that participate in inflammatory reactions. Development of monoclonal antibodies against cell-surface structures that are lineage or subset specific has led to trials of anti-T-cell reagents in RA, but results thus far must be regarded as a significant therapeutic disappointment. A monoclonal antibody designed to interfere with the action of a cytokine, tumor necrosis factor alpha (**TNF-alpha**), has been studied in both open and controlled trials. Treatment with this antibody resulted in marked changes in indices of inflammation, but duration of responses may be limited by the eventual development of antibodies to the anti-**TNF-alpha** antibody. Immunomodulatory strategies that use the immune system to regulate autoimmune activity have been developed based on animal studies, and evaluation of oral collagen as a treatment in RA is currently underway. If successful, this approach would represent a new direction in the treatment of human autoimmune disease. In the future, use of gene therapy directed to the joint could be a powerful approach to treatment of RA. Rational use of biological therapies in RA will depend, in part, on improved understanding of the pathogenesis of this

06313672 EMBASE No: 1995351542
Combination therapy
Borigini M.J.; Paulus H.E.
Division of Rheumatology, UCLA School of Medicine, 32-48 Rehabilitation, 1000 Veterans Avenue,Los Angeles, CA 90024 United States
Bailliere's Clinical Rheumatology (BAILLIERE'S CLIN. RHEUMATOL.) (United Kingdom) 1995, 9/4 (689-710)
CODEN: BCRHE ISSN: 0950-3579
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

It is accepted that combination DMARD therapy is a useful tool in current rheumatological practice. However, well-designed, large, long-term, controlled clinical trials are needed to determine which combinations, dosage schedules, and sequences of administration are most beneficial and least toxic. Until we develop treatment regimens that reliably induce and sustain acceptable control of disease manifestations in all patients for the rest of their natural lifespan, daily oral prednisone will continue to be a troublesome component of 'bridge' therapy, as it becomes the sole surviving constant in complex regimens whose other components are eventually discontinued because of toxicity, lack of efficacy, or non-compliance. We have often seen patients in whom the replacement of a well-tolerated but presumable ineffective DMARD with another DMARD has led to worsening of disease, when the modest benefits of the discontinued DMARD were lost before the hoped for onset of benefit from its replacement became evident. Since the toxicity of combinations of DMARDs has not appeared to be excessive, one can reasonably add the second DMARD to the first, while carefully monitoring for adverse effects and planning to continue the combination until increased benefit occurs. Subsequently, if the second DMARD is not tolerated, the partial benefit from the first has not been given up, and a longer duration of treatment with the initial DMARD is sometimes associated with satisfactory improvement. If better control of rheumatoid **arthritis** is evident after 3-6 months of treatment with the combination of DMARDs, one must still decide whether to stop the first DMARD, stop the second, or continue with the combination. In the absence of major toxicity, we are most likely to choose to continue the combination if the patient has had a good response, thus inadvertently embarking on prolonged combined DMARD therapy. Of course, other drugs besides those discussed above are available to control different aspects of joint damage; they should be considered in any combination therapy. Drugs which potentially protect cartilage from damage, such as orgotein, glycosaminoglycan polysulphate (Arteparon), and Rumalon, may prove useful in rheumatoid **arthritis**; they have been studied in osteoarthritis, but there is evidence that they protect cartilage from breakdown by inflammation in some animal models. As one of the many goals of treatment in rheumatoid **arthritis** is to protect cartilage, these chondroprotective agents might also be considered as part of the combinations to be studied. The combination of modest clinical efficacy with minimal toxicity reported with minocycline treatment of rheumatoid **arthritis** make this another potentially interesting addition to combination therapy regimens. It is also important to continue the development of so-called 'biological agents', such as interleukin-2 receptor antibodies, anti-CD4 antibodies, anti-**TNF-alpha** agents and antithymocyte globulin. Combinations which include such agents have not yet been evaluated, although it seems logical considering that these agents

offer the possibility of precise intervention directed at specific steps of the immuno-inflammatory process; their combination may thus be more effective than the use of single agents alone. While we await results of well-designed studies of these newer agents in RA therapy, we should continue to consider creative ways of using drugs that are already available.

9/7/8 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

06313672 EMBASE No: 1995351542
Combination therapy
Borigini M.J.; Paulus H.E.
Division of Rheumatology, UCLA School of Medicine, 32-48 Rehabilitation, 1000 Veterans Avenue,Los Angeles, CA 90024 United States
Bailliere's Clinical Rheumatology (BAILLIERE'S CLIN. RHEUMATOL.) (United Kingdom) 1995, 9/4 (689-710)
CODEN: BCRHE ISSN: 0950-3579
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

It is accepted that combination DMARD therapy is a useful tool in current rheumatological practice. However, well-designed, large, long-term, controlled clinical trials are needed to determine which combinations, dosage schedules, and sequences of administration are most beneficial and least toxic. Until we develop treatment regimens that reliably induce and sustain acceptable control of disease manifestations in all patients for the rest of their natural lifespan, daily oral prednisone will continue to be a troublesome component of 'bridge' therapy, as it becomes the sole surviving constant in complex regimens whose other components are eventually discontinued because of toxicity, lack of efficacy, or non-compliance. We have often seen patients in whom the replacement of a well-tolerated but presumable ineffective DMARD with another DMARD has led to worsening of disease, when the modest benefits of the discontinued DMARD were lost before the hoped for onset of benefit from its replacement became evident. Since the toxicity of combinations of DMARDs has not appeared to be excessive, one can reasonably add the second DMARD to the first, while carefully monitoring for adverse effects and planning to continue the combination until increased benefit occurs. Subsequently, if the second DMARD is not tolerated, the partial benefit from the first has not been given up, and a longer duration of treatment with the initial DMARD is sometimes associated with satisfactory improvement. If better control of rheumatoid **arthritis** is evident after 3-6 months of treatment with the combination of DMARDs, one must still decide whether to stop the first DMARD, stop the second, or continue with the combination. In the absence of major toxicity, we are most likely to choose to continue the combination if the patient has had a good response, thus inadvertently embarking on prolonged combined DMARD therapy. Of course, other drugs besides those discussed above are available to control different aspects of joint damage; they should be considered in any combination therapy. Drugs which potentially protect cartilage from damage, such as orgotein, glycosaminoglycan polysulphate (Arteparon), and Rumalon, may prove useful in rheumatoid **arthritis**; they have been studied in osteoarthritis, but there is evidence that they protect cartilage from breakdown by inflammation in some animal models. As one of the many goals of treatment in rheumatoid **arthritis** is to protect cartilage, these chondroprotective agents might also be considered as part of the combinations to be studied. The combination of modest clinical efficacy with minimal toxicity reported with minocycline treatment of rheumatoid **arthritis** make this another potentially interesting addition to combination therapy regimens. It is also important to continue the development of so-called 'biological agents', such as interleukin-2 receptor antibodies, anti-CD4 antibodies, anti-**TNF-alpha** agents and antithymocyte globulin. Combinations which include such agents have not yet been evaluated, although it seems logical considering that these agents

offer the possibility of precise intervention directed at specific steps of the immuno-inflammatory process; their combination may thus be more effective than the use of single agents alone. While we await results of well-designed studies of these newer agents in RA therapy, we should continue to consider creative ways of using drugs that are already available.

10067401 BIOSIS NO.: 199598522319
Effect of **methotrexate** alone or in combination with sulphasalazine on the production and circulating concentrations of cytokines and their antagonists: Longitudinal evaluation in patients with rheumatoid **arthritis**.
AUTHOR: Barrera P(a); Haagsma C J; Boerbooms A M Th; Van Riel P L C M; Borm G F; Van De Putte L B A; Van Der Meer J W M
AUTHOR ADDRESS: (a)Dep. Rheumatol., University Hospital Nijmegen, PO Box 9101, 6500 HB Nijmegen**Netherlands
1995
JOURNAL: British Journal of Rheumatology 34 (8):p747-755 1995
ISSN: 0263-7103
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: In a recent study from our group, the combination of **methotrexate** and sulfasalazine (MTX + SASP) seemed superior to MTX alone in the treatment of rheumatoid **arthritis** (RA). To assess the impact of these therapies on the cytokine cascade, the in vitro production and circulating concentrations of several cytokines and endogenous cytokine antagonists were measured in 30 healthy controls and longitudinally in a subset of 26 patients enrolled in this study. Compared to controls, RA patients had significantly higher circulating concentrations of interleukin-6 (IL-6), soluble receptors for tumour necrosis factor (sTNFR), soluble receptors for interleukin-2 (sIL-2R) and interleukin-1 receptor antagonists (IL-1RA), and their peripheral blood mononuclear cells (PBMNC) showed a higher spontaneous production of interleukin-1-beta (IL-1-beta), tumour necrosis factor alpha (**TNF-alpha**) and IL-1RA (both secreted and cell-associated) and a higher stimulated production of cell-associated **TNF-alpha**, IL-1RA and (to a lesser extent) IL-1-beta. Treatment with MTX alone (n = 12) or combined with SASP (n = 14), resulted in significant reductions of circulating IL-6 and sIL-2R but did not alter IL-1-beta, **TNF-alpha** or IL-1RA concentrations. Decreases in circulating levels of sTNFR and in the in vitro production of cell-associated IL-1-beta and IL-1RA after stimulation were only observed in patients treated with MTX+SASP. The concentrations of IL-1RA and sTNFR in the circulation exceeded moderately those of IL-1-beta and **TNF-alpha** but this is probably insufficient to block IL-1 and **TNF-alpha** activity. In conclusion, therapy with MTX alone or with SASP modulates I L-6 and sIL-2R concentrations in RA. Decreased production of I L-1-beta and IL-1RA and circulating sTNFR levels were only observed during therapy with MTX + SASP. Whether this relates to the better clinical effect observed with the combination therapy remains to be investigated. Circulating levels of IL-6, sIL-2R and sTNFR seem useful markers of

9/7/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10080567 BIOSIS NO.: 199598535485
Tumor necrosis factor alpha (**TNF**) blockade enhances **methotrexate** (MTX) response in patients with rheumatoid **arthritis** (RA).
AUTHOR: Sander Oliver; Herborn Gertraud; Rau Rolf
AUTHOR ADDRESS: Rheumatol. Unit, Evangelisches Krankenhaus, D-40882 Ratingen**Germany
1995
JOURNAL: Arthritis & Rheumatism 38 (9 SUPPL.):pS266 1995
CONFERENCE/MEETING: 59th National Scientific Meeting of the American College of Rheumatology and the 30th National Scientific Meeting of the Association of Rheumatology Health Professionals San Francisco, California, USA October 21-26, 1995
ISSN: 0004-3591
RECORD TYPE: Citation

9/7/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10080568 BIOSIS NO.: 199598535486
Suppression of tumor necrosis factor (**TNF**) and **TNF**-mediated effector mechanisms by **methotrexate** (MTX) in patients with rheumatoid **arthritis**.
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Set	Items	Description
S1	441	(TNF OR TNF(W)ALPHA OR TNFALPHA) AND METHOTREXATE
S2	273	RD S1 (unique items)
S3	11	S2 AND PY=1991
S4	153	S2 AND (ARTHRITIS OR CROHNS)
S5	5	S4 AND PY=1991
S6	1	S4 AND PY=1992
S7	6	S4 AND PY=1993
S8	5	S4 AND PY=1994